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CLINICAL PROCEEDINGS

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CHILDREN'S HOSPITAL

WASHINGTON, D. C.

May 1954

VOLUME X NUMBER 5

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OF THE CHILDREN'S HOSPITAL

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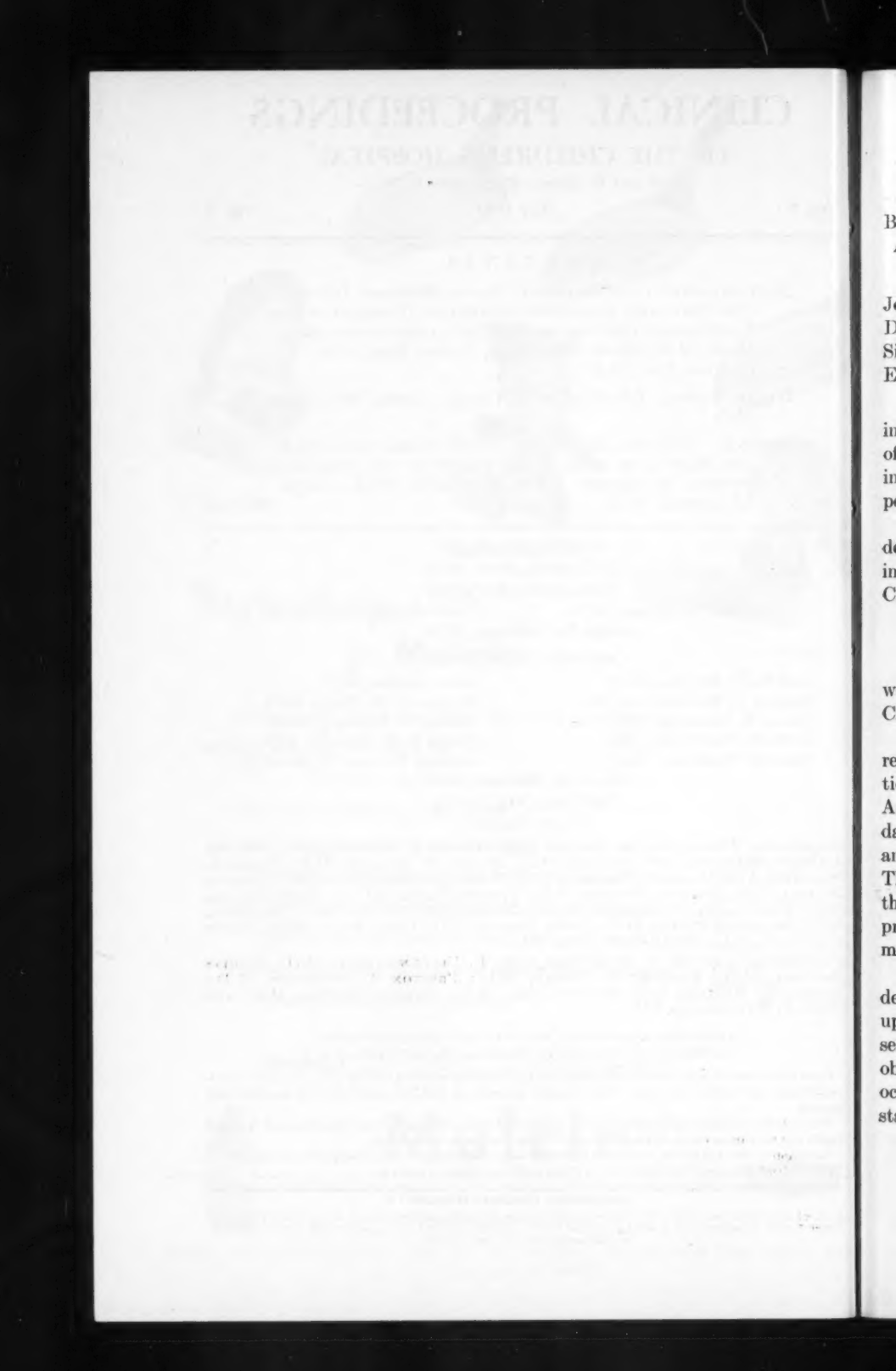

BONE MARROW AND PERIPHERAL BLOOD STUDY OF INFANTS AND CHILDREN RECEIVING ANTIBIOTIC THERAPY WITH PARTICULAR REFERENCE TO CHLORAMPHENICOL

John Doyle, M.D.
David Bell, M.D.
Sidney Ross, M.D.
E. Clarence Rice, M.D.

There have been several articles in the recent medical literature regarding bone marrow depression, presumably resulting from the administration of chloramphenicol[1, 2, 3, 4]. In many instances reported, the drug has been incriminated in retrospect since very few early or control studies, either on peripheral blood or bone marrow, were done on these patients.

In June, 1952, a study was initiated at Children's Hospital designed to determine whether or not early blood or bone marrow depression occurred in a controlled group of patients receiving therapeutic doses of antibiotics. Chloramphenicol was the principal antibiotic administered.

METHODS AND MATERIALS

Forty-three patients in the pediatric age group (4 days–12 years) who were admitted to the Diarrhea Service and the Meningitis Ward of the Children's Hospital were studied.

A complete peripheral blood count (hemoglobin, reticulocytes, platelets, red blood cells, white blood cells, and differential) and bone marrow aspiration were done on admission before any type of therapy was instituted. An antibiotic or combination of antibiotics was then given for a full ten day period. The peripheral blood was studied completely every second day and another bone marrow examination was done ten days after admission. The peripheral blood was examined six to eight weeks after discharge from the hospital. An attempt was made to ascertain any history of allergy or previously demonstrated drug sensitivity to either the patient or the immediate family.

The technique of bone marrow aspiration employed was similar to that described by Sturgeon[5, 6, 7]. Tibial marrows were obtained from patients up to the age of twenty months after which age sternal and iliac sites were selected. A Schleicher needle was used for aspirating and the buffy coat, obtained after centrifugation of heparinized marrow in a Wintrobe hematocrit tube, was smeared and stained by freshly filtered domestic Wright's stain. In addition, bone marrow particles were obtained on all cases by the

From the Research Foundation of Children's Hospital, Washington, D. C.
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method described by Schleicher[8] and random case samples of these particles were prepared as tissue slides and stained with hematoxylin and eosin. Cytological ratios of this material closely coincided with those counted on smears prepared from the centrifuged marrow. Therefore, the results of the smears were recorded and the fixed particles obtained and saved only for reference or complete study of any indicated case.

Three ratios of marrow cells were determined in all cases and in some cases a fourth ratio was counted. The ratios used in evaluation were as follows:

1. Myelocytic series
   Immature myelocytes/polymorphonuclear and stab forms/eosinophiles
2. Myelocytic/Lymphocytic Ratio
3. Lymphocyte/Plasma Cell Ratio
4. Pronormoblasts/Normoblasts Ratio

The ratios were counted and the bone marrows evaluated without knowledge of the specific antibiotic therapy employed in any given case. The clinical and bacteriological diagnoses were known.

TABLE 1

	C	T	A	P	S	NO THERAPY
Non-specific diarrhea (24 cases)	15	2	2	3	2	4
Shigella (11 cases)	9	0	2	0	2	0
Salmonella (4 cases)	4	0	0	0	0	0
Influenzae meningitis (4 cases)	4	0	2	0	0	0

Code:
C—Chloramphenicol
T—Terramycin
A—Aureomycin
P—Penicillin
S—Sulfadiazine

TABLE 2

DRUG	DOSAGE
Chloramphenicol	
Palmitate	150
Intravenous	75–100
Intramuscular	100
Aureomycin	75
Terramycin	75
	Mgm/kgm/day
Penicillin	300,000 U to 1,000,000 U/day
Sulfadiazine	1.0–2.5 grains/lb/day

Table 1 shows the number of cases receiving the different antibiotics arranged according to diagnosis.

Table 2 lists the drugs used and the dosages employed over the ten day period in the present study.

RESULTS

Due to the nature of the diseases affecting the 43 patients in the group studied, the bone marrow smears showed fairly definite characteristics for the three major types of cases. In general, the differences between the initial bone marrow and the ten-day bone marrow specimen are listed in table 3 and may be described as follows:

1. Non-specific diarrhea (24 cases)
   Some maturation of granulocytes in the ten-day specimen was seen with rare cases showing a marked increase in mature granulocytes in the ten-day specimen. Rare cases showed a marked preponderance of lymphocytes in the initial specimen. Almost all marrows showed an increase in immature granulocytes in both specimens.
2. Salmonella and Shigella infections (15 cases)
   In contrast to the cases of non-specific diarrhea, most cases showed a very marked and obvious maturation of granulocytes in the ten-day specimen. Many cases showed a preponderance of lymphocytes in the initial specimen. Almost all marrows showed an increase of mature granulocytes in the ten-day specimen.
3. Influenza meningitis (4 cases)
   The marrows of these patients were initially myelocytic, with a marked maturation and preponderance of granulocytes in the ten-day specimen.

Review of the bone marrow ratios and the peripheral blood studies of the 43 cases in this group showed that in none of the patients was there any evidence of bone marrow or peripheral blood depression, regardless of the antibiotic or combination of antibiotics administered in any given case.

Table 3 shows bone marrow ratios (averages), at the time of admission

TABLE 3

	IMM. MYEL	STABS POLY	EOS	MYEL	LYM	LYM	PLASMA	
Admission.....	17	7	0	42	43	97	3	Non-specific diarrhea (24)
10 days later.....	19	34	5	58	38	98	2	cases
Admission.....	19	26	4	48	51	97	3	Salmonella and shigella
10 days later.....	14	48	6	64	34	99	1	enteritis (15 cases)
Admission.....	33	49	18	56	44	95	5	H. Influenzae Meningitis
10 days later.....	24	68	8	87	13	99	1	(4 cases)

and 10 days later after completion of therapy. Similarly, follow-up peripheral blood counts obtained six weeks later failed to show any aberrations from the normal.

It should be noted that thirty-three patients (over 75%) of the total number studied received chloramphenicol either orally, intramuscularly or intravenously.

DISCUSSION

Welch et al[9], in a careful nation-wide survey of the possible deleterious effects of chloramphenicol on bone marrow concluded that in certain susceptible persons, chloramphenicol may cause blood dyscrasias including aplastic anemia, leukopenia, granulocytopenia and thrombocytopenic purpura. The incidence of aplastic anemia following chloramphenicol administration was estimated to be one case in 40,000 patients receiving the drug. Parenthetically, it was pointed out by Welch et al[9] that aplastic anemia may occur following the use of other commonly used drugs such as sulfonamides, other broad spectrum antibiotics, anticonvulsants, antihistamines and antipyretics. In addition, it was observed that there was a nonconstant relationship demonstrable between the occurrence of bone marrow depression and either the dose, duration of therapy, or allergic diathesis of the patient.

In the group under investigation, four of the 43 patients had a suggestive allergic history. None of the children had recieved chloramphenicol prior to its administration in this series.

The present study was undertaken with the full realization that in view of the rarity of bone marrow depression following chloramphenicol administration, it would be highly unlikely that any instance of blood dyscrasia would make its appearance in a relatively small series of cases. On the other hand, it was hoped that the incipient marrow changes might possibly have provided a clue which may have allowed the detection of impending bone marrow depression. However no evidence of deranged hematopoiesis was forthcoming from these cases under study.

In our total experiences in over 2000 cases in the pediatric age group, with all forms of chloramphenicol therapy including the oral, intravenous, and intramuscular preparations, we have encountered sporadic instances of leukopenia and granulocytopenia which were of a transitory nature. Up to the present writing, however, we have not personally encountered a single instance of aplastic anemia.

SUMMARY

1. The object of the present investigation was to determine whether or not early blood or bone marrow depression occurred in a controlled group

of patients receiving therapeutic doses of antibiotics. Chloramphenicol was the principal antibiotic administered.

2. Forty-three patients in the pediatric age group were studied. A complete peripheral blood count (hemoglobin, reticulocytes, platelets, red blood cells, white blood cells and differential) and bone marrow aspiration were done on admission before any type of therapy was instituted. An antibiotic or combination of antibiotics was then given for a full ten-day period. The peripheral blood was studied completely every second day and another bone marrow examination was done ten days after admission. The peripheral blood was examined six to eight weeks after discharge from the hospital.

3. Therapeutic doses of chloramphenicol, aureomycin, terramycin, sulfadiazine and penicillin were employed in the present series. Thirty-three patients (over 75%) received chloramphenicol either orally or parenterally.

4. Review of the bone marrow ratios and the peripheral blood studies of the 43 cases in this group showed that in none of the patients was there any evidence of bone marrow or peripheral blood depression regardless of the antibiotic or combination of antibiotics employed in any given case.

ACKNOWLEDGEMENTS

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WILMS' TUMOR

A Survey of 42 Cases*

Dr. Jerome Bernstein

During the 19 year period from 1934 to 1953, 42 patients with Wilms' Tumor or embryoma of the kidney were treated at the Children's Hospital, Washington, D. C. The diagnosis was proven in most of the patients by microscopic examination of tissue removed at autopsy or operation.

The average age of these patients at the time of diagnosis was 35.7 months. The oldest patient was 12 years of age and the youngest 5 months. A break-down of the ages, sex and color distribution at diagnosis is given in Table I. The presenting signs and symptoms are given in Table II.

Silver[1] reports that abdominal pain was present in about 50 percent of his patients and in several instances it occurred before the abdominal mass was noted. Gross and Neuhauser[2] found pain and discomfort to be uncommon. Hematuria, fever, nausea and/or vomiting were present in approximately 12 percent of the patients included in this report.

Hematological findings were generally within the normal limits for the patients' ages. Blood pressures were recorded so seldom as to be of no value statistically. Silver[1] reported hypertension in seven out of eight patients whose blood pressures were recorded and Goddard[4] found the initial blood pressure readings to be elevated at times. Intravenous pyelography was performed in 37 patients and in most cases this procedure was sufficient to determine the status of the involved kidney and the opposite kidney. In six instances retrograde pyelograms were done to obtain clearer visualization.

The right kidney was involved in 16 patients, the left in 25, and bilateral involvement was noted once.

Prior to the organization of the Tumor Board in 1948, the average time which elapsed between recognition of the tumor and operation for its removal was 23.6 days. Since 1948 the average time elapsed has been 2.3 days.

Nephrectomies were performed in 34 of the 42 patients, the approach being transabdominal in all but one patient. Six of the patients were considered to be inoperable, one having bilateral involvement. The parents of two of the patients refused to permit operation.

Post-operative irradiation was given in most of the patients operated on prior to 1948 and since then all patients operated on have been irradiated. During the past five years irradiation therapy has not been instituted until an average of 4.4 days had elapsed post-operatively despite the recom-

* From the Tumor Clinic and the Department of Laboratories, Children's Hospital, Washington, D. C. The Tumor Clinic is supported by The American Cancer Society.

TABLE I

Age at Diagnosis		*Sex Distribution*	
Less than 1 year	6 (14%)	Male	26
1 year through 4 years	33 (77%)	Female	16
5 years and older	4 (9%)		

Color Distribution	
White	28
Colored	17

TABLE II

PRESENTING SIGNS AND SYMPTOMS	NUMBER OF CASES IN WHICH PRESENT
Abdominal mass	37
Abdominal pain	14
Hematuria	5
Fever	5
Nausea and/or vomiting	4
Pyuria	2

mendation of the Tumor Board that such therapy immediately follow operation. More recently this plan has been followed in nearly all cases. Prior to 1948 the average amount of irradiation has been 2147r and since then the dose over the tumor area has been 2537r. Gross[5] advocated a total of between 4,000 and 5,000r. Given in daily doses of 200r, the first dose to be given on the day of operation.

Post-operative chemotherapy has been recommended by the Tumor Board to supplement surgery and irradiation.

The survival rate at this hospital as compared with the reports of Silver, Gross and Neuhauser, Dickey and Chandler, and Nesbit and Adams leaves much to be desired. Of the 36 patients who were operated on at this institution, 10 are living two or more years following operation, giving a survival rate of 27.7 percent for this group. One of these patients shows evidence of metastases at this time. The overall survival rate is 24 percent.

Silver[1] reported in 1947 a series of 18 patients with 10 survivals of 13 patients who had nephrectomy, a survival of 76.9 percent and an overall

TABLE III

Survival in Relation to Age at Operation

AGE	PATIENTS	LIVING 2 OR MORE YEARS POST-OPERATIVELY
One year or less	6	3 (50%)
Over one year of age	30	7 (23.2%)

survival of 55.5 percent. Gross and Neuhauser[2] in a series of 38 patients from 1940 to 1947 reported a survival rate of 47 percent in children of all ages and in children under one year of age a survival of 80 per cent. Dickey and Chandler[3] reported in 1949 a survival of 33.3 percent in a series of 12 cases. In 1946 a series of 16 patients Nesbit and Adams reported a survival rate of 58.4 percent in 12 of these patients who had had nephrectomies. These rates are based on at least 2 years survivals and in most cases much longer.

Since the formation of the Tumor Board in 1948 there has been an increase in the number of successfully treated patients. The members of the Board acting in an advisory capacity have recommended: (1) that all patients with abdominal tumors have the abdominal examination made by as few persons as possible, (2) that an intravenous pyelogram and other essential examinations be made on the day of admission if possible, (3) that if an abdominal tumor is believed to be present that operations be performed as soon as possible, using the transabdominal approach, (4) that immediate post-operative irradiation be given to all patients with embryomas of the kidney, and (5) that alternate patients receive chemotherapy in addition to the above. It is believed that the improvement in the results obtained have been due largely to the recognition on the part of the pediatrician and surgeon of the desirability of following these recommendations.

SUMMARY

An analysis of the results of treatment of 42 patients with embryoma of the kidney is presented.

The overall survival rate was 24 percent, and of those who underwent nephrectomy the survival rate was 27.7 percent. The survival rate among the patients one year of age or younger was 50 percent.

The need for early recognition, and prompt surgical removal followed by immediate irradiation is urged.

The possible benefit to be obtained from postoperative chemotherapy is suggested.

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ADRENAL HYPERPLASIA WITH PSEUDOHERMAPHRODITISM AND SALT LOSS WITH A DISCUSSION OF THE ADRENOGENITAL SYNDROME

Dr. Robert H. Parrott*
Dr. Joseph M. LoPresti†

INTRODUCTION

The alert physician regularly considers adrenal insufficiency among the possible causes of vomiting in a newborn patient. If his patient is apparently a girl, who shows signs of pseudo-hermaphroditism in addition to vomiting, the physician is led further to investigate adrenal status. Should the infant then evidence hyperkalemia, hyponatremia, acidosis and an elevated urinary 17-ketosteroid excretion, the physician is faced with a relatively clear-cut syndrome, pseudohermaphroditism and salt loss apparently due to adrenal hyperplasia. Such a case is presented here in order to review the clinical diagnosis and the nature of this illness and to discuss the long term therapeutic problem, which is a corollary to the diagnosis and concerning the partial solution of which recent advances have been highly encouraging.

CASE REPORT

R. H.‡: This infant was born of an induced labor on May 3, 1952, five days beyond the expected date of confinement, and weighed seven pounds, three ounces at birth. Physical examination revealed no abnormalities except for the appearance of an enlarged phallus with a common urethro-vaginal outlet. The baby was breast fed; and shortly after the first attempt at feeding, she began to vomit. This continued during the maternity hospitalization. At the age of seven days, the child weighed six pounds, seven ounces. After being placed on an evaporated milk feeding, the child continued to vomit. The vomitus was occasionally yellow, was sometimes projectile, and did not occur immediately following the feedings. The baby also began to have six to seven watery stools a day. Despite several changes in the formula, including a change to a hypo-allergenic milk, the vomiting and diarrhea continued, so that on the twelfth and thirteenth days of life, the baby became hyperpneic and appeared dry and drowsy.

There had been no family history of similar illness. This was the second pregnancy for the parents, the first having terminated in a miscarriage at four months gestation.

When the baby was admitted to the Children's Hospital, Washington, D. C., she was dehydrated, hyperpneic, mildly cyanotic, and showed the genital abnormalities already described.

The initial laboratory work follows:

CO_2 combining power: 31 volumes percent; potassium: 8.4 meq./l; sodium: 124.5 meq./l.; chloride reported as NaCl: 612 mgms./ 100 ml.; BUN: 22.5 mgms./ 100 ml.;

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† Assistant Professor of Pediatrics, George Washington University School of Medicine.

‡ Reported with the permission of the attending pediatrician, Dr. John Peacock. Drs. Samuel Bessman, John Washington and Roy Hertz have been active in the clinical and laboratory management.

TABLE 1

DATE	WEIGHT	CORTISONE DOSAGE	SERUM		COMMENT
			Na (mEq./L)	K (mEq./L)	
5–10			124.5	8.4	Parenteral fluids
5–17	5′13″	15 mgm. IM			
5–18		15 mgm. IM	132.9	5.5	
5–19		15 mgm. IM	132.8	5.6	
5–20	5′3″	15 mgm. IM			
5–21		15 mgm. IM		5.3	
5–24		15 mgm. IM	138.5		
5–28		15 mgm. IM	137.5	3.1	
5–30	7′1″	10 mgm. IM		5.9	
6–2		10 mgm. IM		6.4	
6–3	6′12″	15 mgm. IM	137	5.9	
6–12	7′1″	15 mgm. oral	146	5.7	
6–14	7′4″	15 mgm. oral	143	6.4	
6–16	6′9″	15 mgm. oral	134	8.1	Cyanotic and dehydrated parenteral fluids
6–17		20 mgm. oral			
6–19	6′13″	15 mgm. IM	136	7	
6–21		15 mgm. IM	139	8.7	
6–23		15 mgm. IM	132	8.4	
6–24		30 mgm. IM			
6–26	6′14″	30 mgm. IM		6.5	
6–28		30 mgm. IM	135	6.3	
6–30		30 mgm. IM	138	5.3	
7–3	7′11″	30 mgm. IM	132		
7–5		30 mgm. IM	144	7.7	
7–7		30 mgm. IM		6	
7–8		50 mgm. oral		6.23	
7–11		50 mgm. oral	128.3	8.3	
7–12		100 mgm. oral			
7–14		100 mgm. oral	135.3	7.36	
7–15		50 mgm. IM with 25 mgm. oral	132	7.15	
7–18		50 mgm. IM with 25 mgm. oral	133	6.23	
7–21		50 mgm. IM with 25 mgm. oral	133	6.07	
7–23		50 mgm. IM with 25 mgm. oral	138	6.07	

Summary of cortisone dosage, electrolyte determinations and growth, in first two months of life of infant with adrenal hyperplasia and pseudohermaphroditism with salt loss.

24 hour urinary 17 ketosteroid excretion: 0.8 mgms.; total eosinophil count 838 cells; total eosinophil count after 10 mgms. of ACTH: 507 in one hour and 573 after four hours.

Following the administration of M/6 lactate, other intravenous fluids were given as follows: 5 percent glucose and saline, 90 ml. per kilo; 5 percent glucose in distilled water, 30 ml. per kilo; and 5 percent glucose in protein hydrolysate, 30 ml. per kilo per 24 hours.

Because of the tentative diagnosis of "mixed" adrenal disease or adrenal hyperplasia with pseudohermaphroditism of the salt losing type, cortisone was started in a dosage of 15 mgms. per day intramuscularly. A total of about three grams of sodium chloride in either formula or parenteral fluids was given. Within three days of the above treatment, the baby's hydration improved, vomiting occurred only in small amounts, and the laboratory findings are shown in Table 1.

The patient's progress throughout her first two months of life may also be noted in the above Table 1. During this time, she did well except for a few days around June 16, when salt in the diet had been diminished, when cortisone was being given by mouth in a relatively small dosage during which time the weather was excessively warm. At this time the baby was cyanotic and dehydrated and required parenteral electrolyte correction.

Her serum potassium became elevated and did not revert to even a near normal level until over a week later when cortisone was again administered by the intramuscular route. During this initial hospital stay and the time that the patient was treated with cortisone, the size of her phallus did not increase in proportion with the child's observed growth. Her body symmetry and bone age were consistent with her age. Before discharge from the hospital during the first admission, various methods of administration of cortisone had been attempted. On a dosage of 50 to 100 mgms. per day by mouth, there was not complete control of the electrolyte disturbance. However, when cortisone in the dosage of from 30 to 50 mgms. per day was given intramuscularly, the serum potassium remained slightly above normal limits. The patient was discharged from the hospital on a normal dietary regime for her age, with the addition of about 3 gms. of salt to the formula per day. Her weight at this time was 8 pounds 9 ounces.

Certain accessory findings during this first hospital admission may be pertinent to the total history. For example, following catheterization early in the hospitalization, the child developed a pyuria, and aerobacter aerogenes and streptococcus faecalis were cultured from the urine. Chloromycetin palmitate was administered to the child from May 22 through June 6, both for the above reason and as a prophylaxis against infection enhanced by cortisone administration. Electrocardiograms performed on May 20, June 19 and June 20 were all interpreted as being within normal limits and showed no evidence of hyperkalemia. The dates of hospitalization for this first admission were May 16, 1952 to July 23, 1952.

Immediately following discharge, the baby did well at home until August 10, when slight vomiting and irritability were noted. There were no signs of infection at this time but the child seemed excessively hungry and began to show distribution of excess subcutaneous tissue in the temporal area and the posterior aspect of the neck. The cortisone, which had been given in a dosage of 50 mgms. per day intramuscularly, was stopped. Two days later when the irritability had subsided, cortisone was reinstituted in a dosage of 12.5 mgms. by mouth daily. During this period, salt was maintained in the formula. On August 19, the baby showed mottling of the skin and a serum potassium of 6.8 meq./l.; her electrocardiogram showed tenting of the T

Fig. 1: Facial appearance of Hypercorticism due to excessive cortisone at the age of three months.

waves. On August 21, she developed further cyanosis and vomited twice. At this time she had right otitis media and was treated in the hospital from August 21 to August 25. For the first time now, desoxycorticosterone acetate (DOCA) was administered in a dosage of 2 mgms. intramuscularly each day. When an excess weight gain was noted on August 29, the DOCA was diminished to 1 mgm. per day and the salt in the formula was reduced to approximately 1.5 gms. per day.

On September 23, it was noted that the child's phallus seemed to be enlarging. All signs of hypercorticism having disappeared, cortisone therapy was again started, this time in a dosage of 10 mgms. per day orally, in addition to the DOCA and 1.5 gms. of salt in the formula. In general, the child's clinical course continued to be good on this combination of therapy until approximately December 22, when she developed anorexia. On the night of December 29, the child vomited and showed discoloration of the lower extremities and abdomen. She had bilateral otitis media and pharyngitis and was admitted to the hospital. Following parenteral therapy of fluids, penicillin and DOCA, she improved and was dischar ged from the hospital on January 1, 1953.

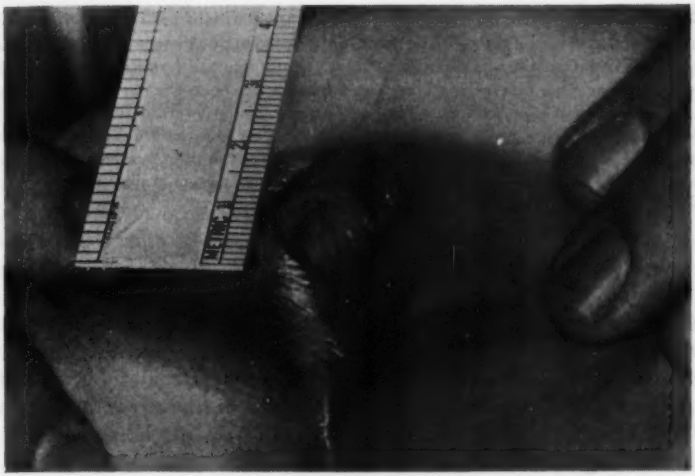

Fig. 2. Enlarged phallus with scrotal appearance to labia when patient was off cortisone therapy.

On January 4, 1953, it was necessary again to admit the child to the hospital because of diarrhea, dehydration and acidosis, due to bilateral otitis media. There was no marked disturbance in the electrolyte balance at this time. She was discharged from the hospital on January 14. A 17-ketosteroid determination at this time on a limited 24 hour urine sample showed the excretion of only 0.6 mgms. per day. The only other hospital admission necessary for this patient was from February 3, 1953 to February 11, 1953, when she again developed bilateral otitis media and pharyngitis. At this time the electrolyte balance, with the exception of the plasma CO_2, was normal. The latter determination was 23 volumes percent at the time of admission and was 37 volumes percent after the administration of M/6 lactate.

After this admission, the child progressed well at home. Her diet was gradually increased commensurate with age, with the addition of approximately 1 to 3 gms. of salt to the milk daily. Until the age of about 21 months, specific therapy included cortisone 5 to 10 mgms. a day by mouth and DOCA 1 mgm. a day intramuscularly. On several occasions, there were episodes of vomiting or diarrhea; usually this occurred when there was also an otitis media. The use of limited oral feeding with a solution containing electrolytes has enabled control of these disturbances adequately.

Because there had never been a diagnostically elevated 24 hour 17-ketosteroid excretion, the cortisone dosage was stopped on May 3, 1953, so that a determination could be made when levels were not influenced by cortisone therapy. On about May 12, 1953, there developed fever and discoloration of the legs of the youngster, and at this time the phallus was larger and erections of the phallus more frequent than usual. Twenty four hour urinary 17-ketosteroid excretion at this time was 3.5 mgms. per 24 hours. The cortisone was again added to the DOCA and salt in the therapy.

At the present time the child has attained and has not surpassed average growth and developmental levels for her age and physique, measured by Wetzel grid, bone age roentgenograms, and Gesell developmental charts. She now requires between

12.5 and 25 milligrams per day of cortisone by mouth. Her need for DOCA has not changed and she presently is being tried on desoxycorticosterone trimethylacetate, a long-acting derivative of DOCA. She shows no evidence of hypertension or intolerance to glucose. One interesting laboratory finding has been that her serum contains extremely low levels of gamma globulin. Urinary 17-ketosteroid levels determined subsequently to those mentioned above have been as high as 9.4 milligrams per 24 hours when cortisone is not administered, and usually under 1 mgm. when proper cortisone dosage is attained. Serum potassium has never recently been over 6 except when DOCA is stopped for trial reasons.

DISCUSSION

Dr. Robert H. Parrott

Rarely is the pediatrician presented with a case such as this, which in itself constitutes an educational exercise in diagnosis, in fluid and electrolyte balance, in pituitary-adrenal physiology, in somatic growth and development, in cortisone and in adrenal cortical derivative therapy and its complications, in problems of infectious disease and immunity, and in problems of guidance for emotional development.

DIAGNOSIS

This baby was presented to the physician in the newborn period as a vomiting infant. The accompanying Table 2 includes a classification of common and uncommon causes of vomiting in the newborn. Clinically in this child there was strong reason to consider one of the rarer etiologies of vomiting, i.e., adrenal insufficiency. The urogenital defect and enlarged phallus suggested that some aberration in urogenital development had occurred relatively early in gestation. This finding, in addition to the progressive vomiting and diarrhea, indicated the presence of a syndrome due to adrenal hyperplasia, wherein there occurs a physiological paradox, namely, excess of adrenal androgenic function and a diminution in adrenal salt and water activity.

TABLE 2

Possible Causes of Vomiting in the Newborn

Feeding problems
Allergy
Intestinal obstruction
Infection
Central nervous system damage
Autonomic imbalance
Renal azotemia
Neoplasms
Metabolic, endocrine disorder
Adrenal insufficiency

Clinical evidence of continued excess androgenic effect in this child is the enlarged phallus which has been observed to become firmer, larger and to undergo erections when cortisone therapy is abrogated. Confirmation of this diagnosis is the demonstration of excess amounts (over 1 milligram for 24 hours in the infant) of urinary 17-ketosteroids. Clinical evidence of lack of salt and water hormone activity is the initial gastro-enteritis and subsequent tendencies to develop vomiting and diarrhea with even mild infections, and a tendency readily to become dehydrated and acidotic when these symptoms are untreated. High serum potassium levels have regularly accompanied such episodes in this youngster. Parenthetically there has been no apparent disturbance in the patient's glucose regulating ability at any time.

This paradoxical adrenal disorder was described first by Butler[1] and Wilkins[2] and others have confirmed the findings as a clinical and pathological entity with remarkable uniformity. Adrenal hyperplasia when it occurs prenatally in females is associated with anomalies of urogenital fusion and an enlarged phallus at birth (pseudohermaphroditism) and in males may include no demonstrable genital abnormality until several months after birth (macrogenitosomia precox). In either sex there may occur a deficiency of adrenal salt and water function. An adrenogenital syndrome occurring post-natally may be due either to hyperplasia of the adrenal cortex or to an adrenal cortical tumor. In explanation of the pathologic physiology of androgenic excess when accompanied by Addison's disease-like salt-losing tendencies, there are several hypotheses:

1) Hyperplasia of a particular type of adrenal cortical cell (zona reticularis) producing androgenic hormone with mechanical "crowding out" of cells which produce the salt-retaining hormone (zona glomerulosa);

2) Abnormal adrenal steroid produced by the hyperplastic adrenal cortex which in addition to androgenic function acts either: A), directly as a salt diuresing or B), as an antagonist to the normal salt retaining effect. Manifestations of this disease have occurred in several members, male or female, of one generation only of a family, indicating that the basic defect is inherited as a Mendelian recessive trait.

TREATMENT

If untreated, a patient such as the one presented would die of dehydration and acidosis. Thus, treatment as for Addison's disease must be employed. In this particular baby, although the diagnosis was made clinically very shortly after admission to the hospital, traditional therapy for Addison's disease was not immediately employed. The child had responded from severe dehydration and acidosis after therapy with salt containing parenteral fluids. It was considered desirable immediately to demonstrate

whether cortisone alone, which as will be pointed out later, is necessary for the treatment of this illness, would also control the salt losing defect. Thus, cortisone alone was employed for the first month or so of the child's life and there was relatively good control of electrolyte disturbance, when large doses were employed. However, it may also be noted in the accompanying table that during most of the time that the child was on cortisone alone her potassium levels remained either high normal or slightly greater than normal, and she did have a tendency to develop, more readily, signs of dehydration and acidosis when infection was present. Thus, although cortisone did partially control the salt losing defect, therapy was much more stable when desoxycorticosterone acetate was added to the therapeutic regime. This experience is consistent with the findings of Crigler in the treatment of these patients[4]. It is interesting that subsequent to the first several months of life when a rather strict administration of determined amounts of salt was attempted, the child has seemingly, within the dictates of her appetite, been able to regulate the amount of salt she needs. For example, at times when she has an infection or gastro-enteritis she desires and takes more than average salt in her milk.

Previous to Wilkins[5, 6] and Bartter's[7] observation that cortisone in proper dosage can arrest the androgenic hyperfunction in a patient with adrenal hyperplasia and the adrenogenital syndrome, there was no treatment for this condition other than that for the salt losing defect. Thus children born with this illness tended to show somatic effects of protein anabolism and masculinization. They would grow rapidly and, skeletally, would have premature closure of the epiphyses which would result in eventual dwarfing. In a female, signs of masculinization were manifest by such defects as are noted in this child with progressive growth of the phallus and with a lack of development at puberty of breast tissue and menstruation. Because of the reports of a favorable effect of cortisone in the treatment of older patients with adrenogenital syndrome, cortisone then was employed early in the therapy for this child. Clinically this drug has been most effective in preventing further masculinization and in preventing abnormally rapid muscular or skeletal growth. It has also been effective in keeping at minimal levels the urinary 17-ketosteroid excretion.

The mechanism of action of cortisone in suppressing the excess androgenic function in this condition is the subject of as much speculation as the question of the real nature of the defect itself. Wilkins[8] postulates that in congenital adrenal hyperplasia the adrenal glands secrete large amounts of estrogen as well as androgen, and that these estrogens cannot exert an end organ effect because of the antagonism of greater amounts of adrenal androgen. However, the estrogen is sufficient to inhibit the secretion of pituitary gonadotropin. In the absence of gonadotropin, the ovaries remain

immature and secrete no female hormones. The administration of cortisone inhibits the secretion of ACTH and thus the hyperactive adrenal androgenic function is decreased. Likewise adrenal estrogen effect decreases, thus permitting the release of pituitary gonadotropin and permitting completion of the endocrine cycle involved in ovarian function. Normal secondary sex development may result. In some way the administration of cortisone also decreases the salt-losing defect which is present in some of these patients.

Determination of the amount of cortisone, DOCA and salt to be employed in such patients as this must necessarily be individualized. However, in a general way it can be said that at least during the first year of life most will be controlled by the administration of from 5 to 25 milligrams of cortisone and from 1 to 2 milligrams per day of DOCA.

The basic electrolyte need during crises of this illness is for sodium chloride per se. Whole adrenal cortical extract should be employed in severe crises just as in the crises of Addison's disease. Again dosage depends upon the need of the patient at the time.

GUIDES TO THERAPY

The clinical guide lines, then, to the condition of such a child include the rate of somatic growth with particular attention to the muscular and skeletal development. They include also observable signs of masculinization such as enlargement of, firmness of, and frequency of erection of the phallus and degree of scrotalization of labial tissues. All of the above signs become more marked when the patient is in poor control regarding androgenic function. One must also be alert to clinical evidences of infection and accompanying dehydration with signs of peripheral vascular collapse. If the physician is able to be in relatively close contact with the patient, it is probably possible without frequent or complicated laboratory determinations to manage a patient within the clinical guide lines mentioned. However, certain laboratory findings are of great value in handling such patients. For example, objective measurement of urinary 17-ketosteroid levels is perhaps the best index of physiologic control of the androgenic function. Likewise helpful are serum electrolyte determinations with particular reference to serum potassium levels which become elevated when water and salt hormone deficiency intervenes. Electrocardiograms may assist in detecting aberrations of potassium levels.

PROGNOSTIC CONSIDERATIONS

The very fact that medical advances have enabled reasonable control of the symptoms of congenital adrenal hyperplasia with salt loss has necessarily created additional interesting questions. We are now concerned,

naturally, with the prognosis not only for the life of this child but for life potential. Presumably, if adequate control of the salt losing defect can be maintained, the child will live. Presumably, also, if a delicate balance can be maintained between cortisone suppression of the androgenic effects and overdosage of cortisone, the child's growth can be normal. Cortisone therapy has induced breast development and menstruation and ovulation in older individuals who have this condition without the salt losing defect. We might then wonder if this child will undergo a relatively normal adolescence, menarch and potential motherhood. If we expect that this will occur, certainly there is a need to consider plastic surgery for correction of the obvious urogenital defect.

One can well imagine the anxiety which must have existed in the minds of the parents of this child, not only concerning her life, whose loss has several times been imminent, but also regarding the question of her sex and her potential for a normal life. Those who have been managing this case have attempted at every opportunity to discuss as fully as possible with the parents her prognosis, and to encourage them to provide as normal an infancy and childhood as possible for this youngster. The very nature of the case has necessitated some degree of protected existence, but for the most part this girl has been enabled to grow emotionally as would any child of a similar age.

Other interesting considerations in her case stem from the probability that the child will have to remain on cortisone therapy most of her life. Certain obvious questions raised by this fact are: what influence has this administration played on the child's susceptibility to infection; what are the probabilities that on cortisone a potentially serious infection may show little or no symptoms; while she is on cortisone, what is this child's ability to develop antibodies against infections to which she is exposed; and will there be a time when intrinsic adrenal cortical ability in the patient will be exhaused as a result of cortisone use? Studies are in progress to determine answers to some of these questions. As noted above, the child does have, by electrophoretic studies, a very low gamma globulin level. Following a series of diphtheria, tetanus and pertussis immunizations she has, however, shown evidence (negative Schick test) of immunity to diphtheria. Future studies will be directed toward determination both of gamma globulin levels and of specific antibody responses following both natural and artificial contact with antigens.

DISCUSSION OF THE ADRENOGENITAL SYNDROME

Dr. Joseph M. LoPresti

It has become increasingly important for the physician of today to acquaint himself with the normal physiology and life-sustaining functions of

the adrenal gland. A knowledge of the normal functions of this endocrine gland is essential for a rational approach to therapy and for the diagnosis of adrenal cortical dysfunction. Secretions of the adrenal cortex usually are considered to comprise three groups:

1. *Steroids which predominantly affect carbohydrate metabolism (11-oxysteroids, and 11,17-oxysteroids).* These substances accelerate conversion of protein to carbohydrate (gluconeogenesis), and enhance the utilization of fat. There is a coincident rise in the blood glucose and liver glycogen store as well as a marked increase in urate excretion. The more active 11 and 17 oxysteroids, of which cortisone is an example, induce lysis of fixed lymphoid tissue, transitory lymphocytopenia, and almost complete disappearance of eosinophilic cells from the circulation. The function of these carbohydrate-regulating steroids may be measured by observing variations in the urinary excretion of 11-oxysteroids, by determining variations in the number of circulating eosinophils, or by determining the urinary uric acid-creatinine ratio.

2. *Steroids which have an electrolyte regulating effect, e.g., 11-desoxycorticosterone.* Retention of sodium and chloride and increased excretion of potassium is induced. Plasma and extracellular tissue volume are coincidentally increased. The measure of the function of these steroids is possible only by indirect methods, e.g., observations of alterations of the mineral content of urine or sweat, changes in blood composition as determined by hematocrit volumes, and variations in body weight.

3. *Steroids especially active as androgens.* These are related in chemical structure to testosterone but have an oxygen group at position 11. They cause masculinization with retention of sodium, potassium, phosphorous, nitrogen, and chlorides. The immediate effects of these steroids can be measured only as reflected in slight increase in urinary 17-ketosteroid excretion.

It is not surprising then that adrenal cortical hyperactivity in children (neoplasm or hyperplasia) may give rise to a variety of symptom complexes due to the excessive secretion of one or more of these adrenal cortical steroids. In the pediatric age group hyperadrenocorticism may be divided into two main groups on the basis of their predominating metabolic manifestations: the adrenogenital syndrome and Cushing's syndrome. In the adrenogenital syndrome there is increased protein anabolism caused by an excessive production of androgen. These patients exhibit excessive masculization, rapid growth in height, marked muscular development, and accelerated epiphyseal ossification. Hypersecretion of the carbohydrate and electrolyte controlling hormones does not occur. As a matter of fact, some patients with the adrenogenital syndrome have crises of acute adrenal insufficiency, i.e., a deficiency of the cortical electrolyte regulating steroids.

In sharp contrast to the adrenogenital syndrome is Cushing's syndrome where there is stunted growth, poor musculature, osteoporosis, and marked obesity. Commonly the glucose tolerance curve is of the diabetic type. This indicates that there is a preponderance of carbohydrate regulating steroid and deficient protein anabolism. Despite this, there is an increased secretion of androgen causing hirsutism and increased output of urinary 17-ketosteroids.

The clinical features of the adrenogenital syndrome depend on the sex of the patient and upon whether the hormonal dysfunction begins in early embryonic life or after the intrauterine differentiation of the sex organs is complete, i.e., before the fifth month of gestation when normal urethral and vaginal relationships have occurred. Excessive androgen production before birth is due to a congenital hyperplasia of the adrenal cortex. If hormonal dysfunction occurs after birth, it may be due either to an adrenal neoplasm or congenital cortical hyperplasia. Congenital hyperplasia of the adrenal cortex in females which becomes manifest before the fifth month of intrauterine life results in a pseudohermaphrodite, whereas, hyperplasia or a neoplasm after the fifth fetal month will produce virilization in the female. On the other hand, in the male, excessive secretion produces macrogenitosomia precox, regardless of the time of onset.

The most common adrenal disorder encountered in childhood is congenital adrenal hyperplasia in the female producing the female pseudohermaphrodite. There are embryologic abnormalities of sex differentiation and evidences of excessive androgen production starting in early infancy. In the fetus, the development of the urogenital system is completed by the fifth month of gestation. In the normal female, the Wolffian ducts disappear and the Müllerian duct system undergoes normal development to form the Fallopian tubes, uterus and vagina. However, the genital duct continues to open into the urethra, forming a persistent urogenital sinus as in the male. Further normal development in the female results in a separate urethra and vagina which open into the vulva. This latter development is complete by the fifth gestational month, and excessive androgen production must occur before this time to produce a female pseudohermaphrodite. If this occurs, there is present an almost uniform and characteristic abnormality of sex differentiation. The labia majora are hypertrophic, while the labia minora are underdeveloped and present as narrow fibrous cords. The clitoris is hypertrophied. This hypertrophic clitoris is bound ventrally by fibrous cords extending backward from the under surface. Between the labia there is a shallow, trough-like depression covered with mucous membrane. The persistent urogenital sinus opens into this, usually with a small orifice resembling the urethral meatus. These clinical features frequently are misdiagnosed as a marked penile hypospadias. Ovaries are present in

these patients. The remaining clinical features of pseudohermaphroditism are the result of excessive androgen production. Somatic growth, muscular development, and epiphyseal ossification become far advanced. Frequently pubic and axillary hair appear by the age of 2 to 5 years. Acne develops early and hypertrophy of the clitoris increases. The voice becomes deep and excretion of 17-ketosteroids is increased. During adolescence, the breasts fail to develop and menstruation does not occur. Epiphyseal fusions occur early and ultimately the patient is a short, stocky, muscular individual.

Congenital adrenal hyperplasia in males produces the syndrome of macrogenitosomia precox. There is a rather high incidence of the adrenogenital syndrome in families where two or more siblings are similarly affected. It is not unusual to find a female pseudohermaphrodite and a male macrogenitosomia precox in siblings. Occurrence of the disorder in more than one generation has not been reported. In some cases the penis is large at birth but often the patient will be 1½ to 3 years of age before there is sufficient growth of the genitalia to attract attention. The penis and prostate attain adult size at an early age. Sexual hair and acne develop early and the voice becomes deep. Despite the marked development of secondary sexual traits, the testes usually remain small and immature and spermatogenesis does not occur. The excretion of 17-ketosteroids is markedly increased (up to 15 mg. per day); The amounts increase progressively. Somatic overdevelopment is striking. Growth is rapid and muscular and osseous development are accelerated. Fusion of the epiphyses occurs early so that complete growth may be attained by the tenth year. Ultimately these are short muscular individuals, the true "infant Hercules." A post-natal adrenal tumor in a male produces similar clinical features and at times, exploratory laparotomy will be the only means of differentiating a neoplasm from hyperplasia. The presence of the disease in a sibling strongly suggests congenital hyperplasia. The finding of a very high output of 17-ketosteroids, particularly the beta fraction, is almost diagnostic of an adrenal tumor. Wilkins reports that when this syndrome is due to hyperplasia, 17-ketosteriod excretion is depressed by cortisone therapy; when due to tumor the 17-ketosteriod excretion is not so affected.

A most important feature of the adrenogenital syndrome which may occur in both males and females is the unique tendency to develop Addisonian-like crises in early infancy. These crises are common and may be precipitated by infections. Weakness, hypotension, and marked anorexia occur. Vomiting and diarrhea are severe. Abdominal pain suggesting an acute abdomen often is present. Dehydration develops rapidly. Marked hemoconcentration of the blood and circulatory collapse ultimately develop. The most constant laboratory findings are an increased non-protein nitrogen due to hemoconcentration, low blood sodium and chlorides, *hyperpotassemia*,

and the presence of large amounts of sodium and chloride in the urine. There is no adequate explanation for the adrenal crises in patients with the adrenogenital syndrome. Pathologically both adrenal glands usually are enlarged diffusely to about 1½ to 3 times their normal size. They frequently have a brownish rather than a yellow color. Microscopically the glands are composed chiefly of large polyhedral granular cells which stain deeply with eosin and resemble the cells of the reticular zone The other zones of the adrenal are diminished or absent. The suggestion has been advanced that salt loss is not due to a lack of electrolyte-regulating steroids but to the secretion of glycogenetic hormones which increase salt excretion. It is also probably so that various aberrations occur in the activities of the corticosteroids.

An adrenal crisis is a medical emergency which requires heroic and early therapeutic measures. Treatment consists of large doses of adrenal cortical extract which is believed to contain a balanced mixture of all the groups of adrenal hormones. In addition it is imperative to give large amounts of salt. In children at least 1 ml. per kilogram of body weight should be given as the initial intravenous dose of the extract and at the same time an additional 5 or 10 ml. should be administered intramuscularly. If there is no response these doses should be repeated in 20 to 30 minutes. During the first 24 hours intramuscular injections of adrenal cortical extract should be repeated every 3 hours in doses of 5 to 10 ml. The early intravenous administration of salt in a dose of 3 to 5 grams daily is essential. A favorable response is manifested by a return of the pulse and blood pressure to normal levels, restoration of the weight loss due to dehydration, and a return to normal of the pattern of serum electrolytes. Treatment with cortical extract should be continued for 2 to 3 days, and then decreased gradually. According to Wilkins, desoxycorticosterone should never be given alone instead of adrenal cortical extract in an acute adrenal crisis as it may produce excessive retention of salt leading to cardiac failure. After the acute crisis has been corrected with cortical extract, and if hydration fails to be maintained adequately, treatment with desoxycorticosterone should be started. This is injected intramuscularly in oil in doses of 1 to 5 mg. per day according to the amount necessary to maintain electrolyte and fluid balance. In addition, a salt intake of 3 to 5 grams daily is an essential feature of the treatment. Cortisone suppresses markedly the excretion of 17-ketosteroids and for this reason, it is indicated in the adrenogenital syndrome, but it should not replace cortical extract or desoxycorticosterone.

SUMMARY

A case of adrenal hyperplasia with pseudohermaphroditism and salt loss is presented. Consideration is given to the diagnosis, pathologic physiology

and treatment of this condition. Several questions regarding the prognosis and future management of this particular case are raised.

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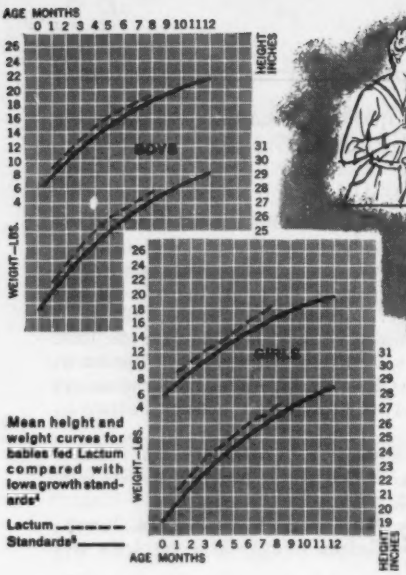
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